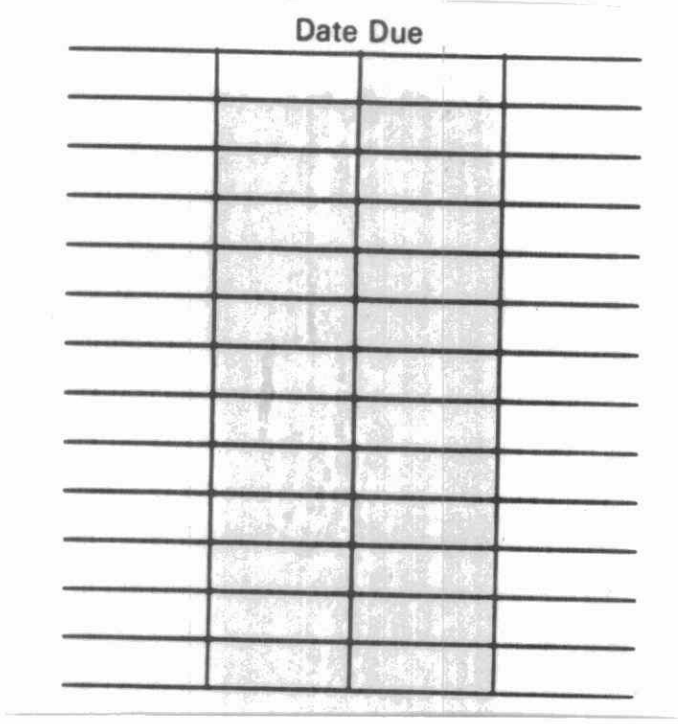
A SCIENTIFIC UPDATE OF THE CURRENT STATUS OF TORDON (PICLORAM) HERBICIDE

PESTICIDES ADVISORY COMMITTEE

Ontario
Ministry of the Environment

Hon. Keith C. Norton, Q.C., Minister

Gérard J. M. Raymond, Deputy Minister



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PESTICIDES ADVISORY COMMITTEE

MINISTRY OF THE ENVIRONMENT

MAY, 1982

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TABLE OF CONTENTS

ONTARIO PESTICIDES ADVISORY COMMITTEE

RECOMMENDATIONS ON PICLORAM

The Ontario Pesticides Advisory Committee, having completed an up-dating review of the new available scientific information dealing with picloram, concludes that picloram poses no new hazard to the natural environment or to human health, and makes the following recommendations:

1. The restricted use of picloram continue under the present permit system to minimize environmental hazard.

2. The restrictions against the use of picloram in agricultural production in Ontario be continued, notwithstanding certain such uses currently acceptable to Agriculture Canada.

3. No further regulatory action against picloram be taken at this time.

4. The monitoring and assessment of new research, as it becomes available, continue.

SUMMARY

1. Picloram (Tordon), when first classified under the Pesticides Act, was placed in Schedule 1 by the Ontario Pesticides Committee because of its potential hazard to non-target vegetation. Its high mobility and persistence in the natural environment were of concern. The registrant and the principal users objected to the scheduling because of the permit requirements which would be necessary for each application. In order that an annual permit could be issued, the product, picloram, was placed in Schedule 2, with a special regulation attending its use (O. Reg. 618/74, s.61(3), now R.R.O. 1980, Reg. 751, s.61(3).). The Company agreed to limit the sale of all picloram products to the holders of permits and report the sales totals to the Pesticides Control Section, Ministry of the Environment on an annual basis. The applicant for a permit must provide a record of the location, rates, total amounts to be used, and the application method.

2. Attention was focused on picloram by an article appearing in the Toronto Star (April 19, 1982) stating that picloram (Tordon) was responsible for increased cancer incidence and death in Cherokee County, North Carolina. It drew attention to two areas of concern: the incidence of cancer in Cherokee County, and Dr. Reuber's re-interpretation of scientific data from a 1978 National Cancer Institute (NCI) report "The Carcinogenicity of Picloram". Subsequently, the Pesticides Advisory Committee undertook a

critical review of the latest scientific literature.

3. A review of the health statistics in Cherokee County done by epidemiologists Carlo and Cook of the Dow Chemical Company indicated that raw unadjusted cancer data were used to obtain the high percentages of increase reported in the newspaper article. It would appear that adjusting the raw data for population size and age and increased level of medical services would alter the calculations considerably. Specifically, the trend in cancer incidence has not varied significantly over the past ten years. Cherokee County is, at present, carrying out a review of the County vital statistics, but the results are not, as yet, available.

4. A paper, dealing with picloram carcinogenicity, was published by Dr. M. D. Reuber in the Journal of Toxicology and Environmental Health May, 1981. This paper did not deal with new experimentation carried out by Dr. Reuber, but was, rather, a review of data released by the National Cancer Institute in "Bioassay of Picloram for Possible Carcinogenicity", and comments on two dog studies carried out by Dow Chemical Company. One of these studies was done by G. E. Lynn in 1965, and the second one by D. D. McCollister and M. L. Leng in 1969. Comments on a rat study carried out by D. D. McCollister and G. E. Lynn in 1969 are also made. Dr. Reuber's publication reviewing the 1978 studies by NCI was not submitted to NCI prior to publication, as is its policy. Because of this and previous actions of Dr. Reuber of a similar nature, the Director of the Frederick Cancer Research Center, Dr. Hanna, wrote a letter to Dr. Reuber admonishing him for acting in a most unprofessional manner and creating

controversies that had both scientific and economic impact. He accused Dr. Reuber of mishandling scientific data and creating public distrust and lack of confidence in the National Cancer Institute (NCI) authorities, who administer the carcinogenesis testing program.

Following receipt of Dr. Hanna's critical letter, Dr. Reuber withdrew one manuscript he had submitted for publication, and requested that other journals that had previously published his papers remove all references to the National Cancer Institute, Litton Bionetics and the Frederick Cancer Research Center.

In May, 1981, the editor of the Journal of Toxicology and Environmental Health published the correction, indicating that the M. D. Reuber paper, "Carcinogenicity of picloram", was reported as an independent study performed by the author, on personal time, and was not endorsed by NCI. Dr. Reuben has since resigned from the NCI Frederick Cancer Research Center.

5. The National Research Council reported that "No tumors were found in male or female mice or male rats at incidences that could be significantly associated with treatment, and it is concluded that picloram was not carcinogenic for B6C3F1 mice or male Osborne-Mendel rats.

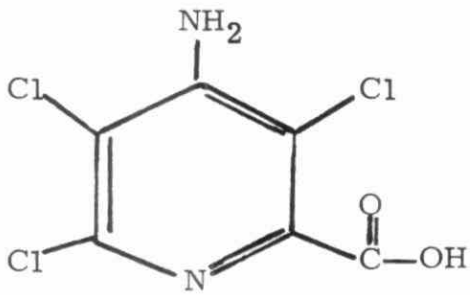
In female rats, however, the incidence of neoplastic nodules of the liver, benign tumors, was associated with treatment with picloram. It is concluded that, under the conditions of the bioassay,

the findings are suggestive of the ability of the compound to induce benign tumors in the livers of female Osborne-Mendel rats." They also reported that "In both males and females, there was a possibly treatment-related lesion of the liver diagnosed as foci of cellular alteration. These latter lesions are frequently associated with the induction of neoplastic nodules and hepatocellular carcinomas in rats." Clarification of these findings is necessary. The animal study is being repeated for this purpose and will be reported in late 1985.

6. No new evidence was found that would indicate that the use of picloram, as currently regulated in Ontario, will create an environmental problem.

PICLORAM

Common name:	picloram
Trade name:	TORDON
Chemical name:	4-amino-3, 5, 6-trichloropicolinic acid
Structural formula:	



Molecular formula:	$C_6H_3Cl_3N_2O_2$
Molecular weight:	241.5
Physical state:	powder
Color:	white
Odour:	chlorine-like
Melting point:	decomposes before melting
Photodecomposition:	subject to photodecomposition but is resistant to ultraviolet irradiation
Vapor pressure:	6.16×10^{-7} mm Hg at 35 C.
	1.07×10^{-6} mm Hg at 45 C.
Solubility at 25°C:	water solubility is 430 ppm, acetone 19,800, ethanol 10,500, kerosene 10 ppm
Formulations: (Used in Ontario)	Tordon 10 K Pellets - 10% picloram as K salt. Tordon 101 Mixture - 60 g/l picloram plus 240 g/l 2,4-D as amine salts.

PHYSIOLOGICAL AND BIOCHEMICAL BEHAVIOUR

Picloram is a selective herbicide which is rapidly absorbed by roots and foliage and translocated within the plant. It is effective on a wide variety of annual and perennial broadleaf weeds and woody species, including many which are resistant to phenoxy herbicides. Most grasses are resistant.

The herbicide is highly phytotoxic. The symptoms of phytotoxicity are similar to 2, 4-D and other phenoxy herbicides - epinasty, cuplike leaves, and tissue proliferation (Klingman, G. C. and Ashton, F. M. 1975).

CLASSIFICATION UNDER THE PESTICIDES ACT

The Pesticides Act and Regulation 751 controls the transportation, storage, sale and use of pesticides in Ontario. All pesticide products must be classified and assigned a schedule and subsequent marketing, and use must be in accordance with the regulations relating to the classification.

Products containing picloram are classified under Schedule 2, a restricted category. In addition, because of previously established environmental concerns, picloram products also require annual use permits and records of location, rates and amounts used in accordance with R.R.O. 1980, Reg. 751, s.61.

Two formulations are currently classified for use in Ontario: -

1. Tordon 10K Pellets containing 10% picloram present as a potassium salt.

2. Tordon 101 Mixture containing 60 grams of picloram amine salt per litre of product and 240 grams of 2,4-D amine salt per litre of product respectively.

PICLORAM USE IN ONTARIO, 1981

Statistics on the amounts used and areas treated in Ontario in 1981 are shown in the accompanying table. Tordon products containing picloram are mainly used by the Ministry of Transportation and Communications (MTC) and Ontario Hydro. Use by the Ministry of Natural Resources (MNR) is relatively minor. Other users in 1981 included Great Lakes Power, Sturgeon Falls Brush Spraying and Cutting Ltd., Canadian Pacific Railways, Trans-Canada Pipelines, and Central Ag. Air Ltd. on contract to C. F. B. Camp Ipperwash.

The Ministry of Transportation and Communications uses Tordon 101 for noxious weed control on selected highways (e.g. Highway 401) in Southern Ontario, and for brush control in Northern Ontario to improve road visibility and to facilitate snow removal programs. In both operations, Norbak, a particulating or thickening agent is used in conjunction with special equipment to minimize the hazard of spray drift. Ontario Hydro uses Tordon 101 to control fast-growing brush species under hydro lines. In addition, in Northern Ontario Tordon 10K is applied on hydro rights-of-way from aircraft to control black spruce and other phenoxy resistant species. The Ministry of Natural Resources uses Tordon to selectively cull undesirable trees. Other users of Tordon use these products to control phenoxy resistant weed species on railway lines, telephone lines and oil and gas pipelines.

TORDON USE FIGURES - 1981 (Subject to minor adjustment)

PERMITS ISSUED TO:	PRODUCT USED	PICLORAM EXPRESSED IN KG ACTIVE INGREDIENT	METHOD OF APPLICATION
1. PROVINCIAL GOVERNMENT AGENCIES			
a) Ministry of Transportation and Communications	Tordon 101	4,130.8	Ground application using a drift control agent
b) Ontario Hydro	Tordon 101	2,884.8	Ground application
	Tordon 10K	153.8	" "
	Tordon 10K	181.4	Aerial application
c) Ministry of Natural Resources	Tordon 101	39.0	Cut surface treatment individual trees selected for treatment
2. OTHER USERS			
a) Great Lakes Power	Tordon 101	10.1	Ground application
	Tordon 10K	567.0	Aerial application
	Sub-total:	7,966.9 C/Fd.	

TORDON USE FIGURES - 1981 (Subject to minor adjustment)

PERMITS ISSUED TO:	PRODUCT USED	PICLORAM EXPRESSED IN KG ACTIVE INGREDIENT	METHOD OF APPLICATION
		B/Fd. 7,966.9	
2. OTHER USERS (CON'T)			
b) Sturgeon Falls Brush Spraying & Cutting Ltd.	Tordon 101	60.0	Ground application
c) C. P. Rail	Tordon 10K	750.0	Ground application
d) Central Ag. Air Ltd. (CFB. Camp. Ipperwash)	Tordon 10K	181.4	Aerial application
e) Trans-Canada Pipeline	Tordon 101	174.3	Ground application
f) C.P. Telecommunications	Tordon 101	9.9	Ground application
	Sub-total:	9,142.5 C/Fd.	

TORDON USE FIGURES - 1981 (Subject to minor adjustment)

PERMITS ISSUED TO:	PRODUCT USED	PICLORAM EXPRESSED IN KG ACTIVE INGREDIENT	METHOD OF APPLICATION
		B/Fd. 9,142.5	
2. OTHER USERS (CON'T)			
g) Northern Central Gas	Tordon 101	82.0	Ground application
h) Ear Falls Airport	Tordon 101	49.9	Ground application
i) Bell Telephone	Tordon 101	23.7	Ground application
	TOTAL:	9,298.1	

PICLORAM

ENVIRONMENTAL IMPACT

GENERAL

Picloram is a wide-spectrum herbicide used in Ontario along the right-of-ways for the control of woody and terrestial broad-leaved plants. Application rates range from 0.1 - 3.3 kg/ha. Right-of-ways for highways, pipelines, railways and power transmission lines are strips of land which average approximately 30 m in width and constitute about 3 hectares per kilometer, or about 3% of a transected km^2. (Selective spot application is practised by Ontario Hydro). Picloram is a compound that is a relatively persistent mobile herbicide which may have several years of residual phytotoxicity. (NRCC Report #13684 1974).

NATURAL ENVIRONMENT

Soil:

The potassium salt of picloram is highly soluble in water (40% w/w), and the solubility of picloram itself is 430 mg/l. It breaks down slowly in temperate climates by the action of soil microorganisms and is not readily adsorbed on soil colloids. The water solubility characteristics of picloram and its salts are the major factors governing its movement and persistence in the soil. The downward, upward or lateral movement of picloram is determined by the mass flow of water which carries it. Dilution in the soil is one of the main reasons for apparent loss in soil. Factors such as moisture content, humidity, water-holding capacity, organic matter, rate of precipitation and temperature are the major considerations in determining the persistence of picloram in the soil.

Water:

As picloram is soluble in water and is not readily absorbed by the colloidal matter in the soil it may be carried by surface runoff to non-target areas such as ponds, lakes and streams. It has been estimated that less than 5% of the total picloram applied to any watershed is actually removed in surface runoff. Residue levels dropped 15% per day for 14 weeks and then decreased less than 1% per day at a rather constant level.

Plants:

Picloram residues in plants decrease rapidly dropping to 10% of the initial zero day level in the first three to four weeks. Residues in plants are higher from foliar application than those found after granular applications. Such residues reach a maximum up to eight weeks after application, and decrease slowly and become non-detectable in one year.

Aquatic Organisms:

Picloram is of low toxicity to fish and such aquatic invertebrates as Daphnia, oysters, shrimps and snails. It does not accumulate in vertebrates or invertebrates in aquatic systems.

Algae and phytoplankton are not affected by low concentrations of picloram in water.

Animals:

The no-effect level of picloram in animals is above 50 mg/kg per day. The no-effect level for birds is 1,000 mg/kg per day, and 500 mg/kg in media for invertebrates.

Japanese quail, bobwhite quail, pheasants, and the mallard duck were fed picloram at several rates for five days and the LC_{50} was found to be above 5,000 mg/kg applied in the feed (Heath, et al., 1972)

Further animal toxicity studies can be found under the Environmental Health Section of this report (pages 16 - 24).

ENVIRONMENTAL HEALTH

INTRODUCTION

The new toxicological data available (1978-82) is very limited, consisting of a paper by M. D. Reuber, a release from the National Cancer Institute (NCI), a short-term mutagenicity test by Carere, et al., and a radioactive picloram study by Nolan, et al. A replacement study on mice and rats, as requested under the IBT requirements, has been started, but will not be completed until 1985. It is understood that interim reports are being submitted to Health and Welfare Canada.

In 1981, Dr. Reuber's review paper was published by the Journal of Toxicology and Environmental Health. It was claimed that he had misrepresented his work as being performed under the auspices of the Frederick Cancer Research Center (FCRC), and had evaded the NCI internal peer review system required for papers submitted for publication. Subsequently, Dr. Reuber was publicly censured by the Director of FCRC for unprofessional conduct and other "obstreperous actions", (anon. 1981). Serious doubt was cast on his interpretation of the NCI slides. Dr. Reuber resigned from FCRC shortly after this public censure. He also wrote the editor of the Journal of Toxicological and Environmental Health asking that all references suggesting endorsement by NCI be removed. These changes were published as an erratum in the May 1981 issue of that journal.

Acute Toxicity:

Picloram has a low acute oral toxicity. The LD_{50} in rats ranges from 5,000 mg/kg body weight to 10,300 mg/kg body weight (Olson, 1963). The LD_{50} for young mallard ducks was reported to be 2,000 mg/kg body weight, and for pheasants the oral LD_{50} (90.5% pure) was reported to be

over 2,000 mg/kg/bw (Tucker and Crabtree, 1970). It has been generally accepted by toxicologists that any chemical with an LD_{50} of 5,000 mg/kg or greater is essentially non-toxic on an acute basis (Loomis, 1978).

In several acute studies, sheep and calves were found to tolerate up to 720 mg/kg and 540 mg/kg respectively of picloram without exhibiting any evidence of toxicity (Lynn, 1965; Jackson, 1965).

Ninety Day Studies:

Ninety day subchronic toxicity studies were carried on male and female rats to determine the no-effect level. A concentration of 0.1% of the diet (equal to approximately 50 mg/kg/bw/day) was found to have no effects based on mortality, body weight, food consumption, hematology, clinical chemistry and terminal organ weight to body weight ratios. At 1.0% of diet, histopathological changes in the liver and in the kidney were observed. There were some similar changes at 0.3% of the diet, but mainly in female rats. Nothing was noted at 0.1% of the diet. (Beatty, et al., 1962).

It was also reported that male and female rats fed the equivalent to 0.16% of the acid for 90 days showed no toxic effects. No changes in general appearance, behaviour, growth, mortality, food consumption, hematology, clinical chemistry, final body and organ weights. Gross and histopathologic examinations of the tissues were negative (Lynn, 1965; McCollister and Leng, 1969).

Dog - Two Years Feeding:

Beagle dogs were fed 15, 50 or 150 mg/kg/bw/day of picloram for two years. Body weight, food consumption, behaviour, mortality, hematology,

clinical chemistry and urinalysis were all normal. There were no gross or microscopic changes attributable to picloram in tissues of any animal sacrificed after being on the diet for one or two years (Lynn, 1965; McCollister and Leng, 1969).

Sheep:

Yearling sheep fed diets containing 18 mg/kg/bw/day of technical picloram for 33 days or Tordon 22K at 72 mg/kg/bw/day acid equivalent for 30 days showed no toxic signs or adverse effects on growth (Jackson, 1965).

Dermal Studies:

Albino rabbits exposed for 24 hours to graded doses of picloram as a suspension under an impervious cup showed no mortality or toxic signs even up to 4 g/kg/bw. There was a slight edema and deep-brown discoloration of the exposed sites (Lynn, 1965).

Cotton pads, one inch square, and dipped in undiluted picloram product were applied ten times over a period of 14 days to clipped abdominal skin of three rabbits. These pads were secured by bandages. Slight hyperamia and edema of the treated areas resulted. One animal developed a very small eschar. All exposed skin returned to normal in 21 days (Lynn, 1965).

Inhalation Studies:

No adverse effects were observed during or for two weeks following the exposure of male and female rats to a saturated atmosphere of a picloram product for a period of seven hours (Lynn, 1965).

Eye Irritation Studies:

Both pure and technical picloram were applied to the conjunctival sacs of the eyes of albino rabbits. Each produced a slight-to-moderate

conjunctivitis. This condition cleared up in seven days. Some very slight corneal cloudiness was also noted in the eyes treated with picloram products but all signs of this injury resolved in a 24 - 48 hour period following application (Lynn, 1965).

Pharmacokinetics and Metabolism:

Studies have shown that picloram is rapidly eliminated from rats unchanged via the urine route. It was also noted that picloram was not metabolized to any extent by the rat. Over 75% of the intravenously administered radioactively labeled picloram was excreted within the first six hours after treatment. After 48 hours, the concentration of the labeled material in all tissues except the genital urinary tract was at or below the limit of detection (Nolan, et al, 1980).

Mutagenicity:

Picloram was not shown to be mutagenic in the Ames test using Salmonella typhimurium with and without S 9, but gave positive results using Streptomyces coelicolor. (Carere, et al., 1968). Picloram was scheduled for testing in the Salmonella mutagenesis assay in field year 1981 by the U.S. National Toxicological Program. Picloram is still undergoing investigation for mutagenicity and a report is expected by the end of 1982.

In an in vivo cytogenetic study, rats dosed with up to 2,000 mg. picloram/kg/bw showed very few chromosomal or chromatid aberrations of bone marrow cells 24 hours later. There was no significant difference between sexes or among dose groups.

Teratogenicity and Reproduction:

Groups of albino rats were fed picloram at levels up to 3,000 ppm (0.3%) in their diet through a three-generation (two litters per generation) period. Fertility, reproduction and lactation studies gave no evidence of adverse effects at any of the treatment levels administered. The indices used were fertility, gestation, viability, lactation, body weight, and the teratological examination of fetuses. (McCollister, et al., 1967).

Groups containing 35 Sprague-Dawley-derived strain of rats were given an oral suspension of picloram in corn oil at the dose of 0, 500, 750 and 1,000 mg/kg/bw on days 6 to 15 of gestation. Pups were delivered by normal parturition or by Caesarean section day 20 of gestation. Toxic signs and mortalities of 14 to 25% between days 7 and 17 were noted in dams at and above 750 mg/kg/day. Visceral and skeletal examinations

of fetuses revealed increased incidence which were not consistently dose-related of (a) unossified fifth sternebrae and bilateral hydroureter in all treated groups; (b) bilateral accessory ribs and unilateral hydroephrosis at 1,000 mg/kg/day; (c) unilateral hydroureter at both 750 and 1,000 mg/kg/day. Megaesophagus and persistent right fourth aortic arch in one fetus and slightly distended lateral cerebral ventricle and flattened ovaries and fallopian tubes in another were observed among 78 fetuses examined from dams at 1,000 mg/kg/day. Both of the affected fetuses were litter mates. Evidence of adverse effects on other parameters studied was not apparent at either 500 or 750 mg/kg/day. Overall effects are more likely to be due to maternal stress than to teratogenic potential (McCollister and Leng, 1969).

Carcinogenicity:

The following reports were reviewed:

(i) National Cancer Institute (NCI) Report.

(ii) Reuber Report.

(iii) Environmental Protection Agency (EPA) Response.

(iv) Media Report by Journalist Keith Schneider.

(v) Cherokee Health Statistics Report issued by Carlo and Cook.

(i) National Cancer Institute Report

In 1978, the United States Department of Health, Education and Welfare issued the publication "Bioassay of Picloram for Possible Carcinogenicity". This was a report from the Carcinogenesis Program carried out by the Division of Cancer Cause and Prevention, National

Cancer Institute (NCI), Bethesda, Maryland. The actual study was carried out by Gulf South Research Institute, New Iberia, Louisiana under direct contract to NCI and under a subcontract to Tracor Jutco, Inc., prime contractor for the NCI carcinogenesis bioassay program.

Technical grade picloram was added to the feed for Osborne-Mendel rats and B6C3F1 mice.

Groups of 50 rats and 50 mice of each sex were fed picloram in the diet at one of the following doses for 80 weeks. Time-weighted average doses for the rats were 7,437 or 14,875 ppm; those for mice were 2,531 or 5,062 ppm. The rats were then observed for 33 weeks and the mice for 10 weeks. All surviving rats were killed at 113 weeks; all surviving mice were killed at 90 weeks. Survival was adequate for meaningful statistical analyses of the incidence of tumors in rats and mice of both sexes.

Mean body weights of high-dosed rats were lower than those of the matched controls during early part of study, however, after 80 weeks, the mean weight of the controls was slightly lower than those of the treated animals. Body weights of the mice were unaffected by picloram.

In rats, a relatively high incidence of follicular hyperplasia, C-cell hyperplasia, and C-cell adenoma of the thyroid occurred in both sexes. Statistical tests for adenoma did not show sufficient evidence for association of the tumor with picloram administration.

There was increased incidence of hepatic neoplastic nodules in treated male and female rats. This lesion, however, is considered to be a benign tumor. In male rats the lesion appeared in only three animals of the low-dose treatment group and was not significant when compared with the controls.

However, the test for positive dose-related trend in females was significant and in the incidence in the high-dose group was significant when compared with that in the pooled-control group.

There was also one hepatocellular carcinoma in a low-dose male rat and one in a high-dose female rat. In both males and females there was a possibly treatment-related lesion of the liver diagnosed as foci cellular alteration. Thus, there is some evidence that picloram affected the livers of rats of both sexes, but more particularly, those of the female.

No tumors were found in male or female mice or male rats at incidences that could be significantly associated with treatment, and it is concluded that picloram was not carcinogenic for B6C3F1 mice or male Osborne-Mendel rats.

It was further reported that "In female rats, however, the incidence of neoplastic nodules of the liver, benign tumors, was associated with treatment with picloram. It is concluded that, under the conditions of the bioassay, the findings are suggestive of the ability of the compound to induce benign tumors in the livers of female Osborne-Mendel rats."

The study is presently being re-run and results will be available in 1985 (National Cancer Inst. 1978).

(ii) Reuber Report:

Two studies of the carcinogenicity of picloram (NCI Report and Dow Chemical Report) were reviewed by Dr. M. D. Reuber. He reported that his examination of the histological sections of the NCI studies indicated that picloram is highly carcinogenic in mice and rats. Neoplasms at all sites, including malignant neoplasms were increased in male and female rats given both low and high dosages of picloram, according to Reuber's findings. The malignant neoplasms were both carcinomas and sarcomas. Reuber reported that carcinomas were observed in the adrenal, thyroid, and pituitary glands of the female rats. Neoplasms were also

increased in the liver of male and female rats and in the reproductive organs of the females. There were also toxic changes in rats and mice. Male rats had chronic renal disease, parathroid hyperplasia, and polarteritis. There was atrophy of the testes in both male rats and mice given picloram.

In 1981, Dr. Reuber's review paper was published by the Journal of Toxicology and Environmental Health. It was claimed that he had misrepresented his work as being performed under the auspices of FCRC and had evaded the NCI internal peer review system required for papers submitted for publication. Subsequently, Dr. Reuber was publicly censured by the Director of FCRC for unprofessional conduct and other "obstreperous actions". Serious doubt was cast in his interpretation of the NCI slides. Dr. Reuber resigned from FCRC shortly after this public censure. He also wrote the editor of the Journal of Toxicology and Environmental Health asking that all references suggesting endorsement by NCI be removed. These changes were published as an erratum in the May (1981) issue of that journal.

(iii) Environmental Protection Agency (EPA) Response

Private communications with EPA officials revealed that EPA pathologists re-examined the slides and confirmed the findings of the original NCI report. Questions were raised about (a) the portion of the NCI study concerning the incidence of hepatic neoplastic nodules in female rats, (b) the use of excessive doses of picloram which induced mortality before termination of the study, and, (c) the use of pooled controls. Dow Chemical, U.S.A., is presently re-running this part of the study with respect to female rats.

(iv) Media Report by Journalist Keith Schneider:

Various picloram formulations were reported in the Inquiry Magazine, March 15, 1982, to have contributed to the increase in the number of cancer related deaths in Cherokee County, North Carolina. It was alleged that picloram was the causal agent for this increase. It was claimed that a 60% increase in death by cancer occurred in Cherokee County between 1977-1980 and that the increase was also twice that of the state average. (Schneider, K., Inquiry Magazine, March 15, 1982, and Toronto Star, April 19, 1982).

(v) Cherokee Health Statistics Report:

Cherokee Health Statistics report April 2, 1982, issued by Carlo and Cook, indicated that "All Causes" and "All Malignancies" mortality information was reviewed. In summary, they concluded that the cancer situation in Cherokee County was seen to be very similar to that which would be expected based on national estimates. (Adjusted data show the cancer rate below national and state level in seven of the ten years, being higher by up to 9% in 1974, 1979 and 1980). The increases found in 1974, 1979 and 1980 were not thought to be appreciable increases. The opening of the new large medical hospital and the increase in the number of doctors has elevated the level of medical services in the county. The cancer information used in the magazine Inquiry and reported in the Toronto Star on April 19th, 1982, was based on raw data which should have been adjusted to take into account changes in population size and age prior to use. For example there has been, and still is, a great influx of elderly people who move to Cherokee County for retirement. (Carlo, G. L., and Ralph R. Cook, 1982).

Cherokee County is at present carrying out its own review of the county's vital statistics, but the results are not, as yet, available.

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A12/ TORONTO STAR, MONDAY, APRIL 19, 1982

THE INSIGHT PAGE

Herbicide raises new cancer fears

It's called Tordon, it's very powerful, it's used widely and the people of Cherokee County say it's killing them

By Keith Schneider
Star special news service

Beneath the majestic mountain beauty of Cherokee County, N.C., lies ugliness. The ugliness is cancer.

Six years ago, one in seven people who died in Cherokee County did so from cancer. Three years later, the rate had jumped to nearly one in four, 60 per cent above the U.S. national average and almost double that of the state.

The primary suspect is an agricultural chemical called picloram, developed by Dow Chemical Corp. in 1963 and now one of the four major products sold by Dow's agricultural chemicals division. Picloram is contained in a line of powerful herbicides marketed under the trade name Tordon.

The U.S. Army took it to Viet Nam, where it was known as Agent White, and sprayed it from tanker planes to kill plants that survived the onslaught of Agent Orange, another powerful herbicide.

Today, millions of pounds of Tordon are poured on North America each year as its popularity as a broad leaf weed and woody brush killer grows. Railways use it to keep roadbeds clear. Highway departments spray it on medians and shoulders instead of mowing. Electric power companies spray it from the air on their power line rights-of-way to hold weeds down. The U.S. Forest Service and America's timber companies use Tordon to trim pine stands of uneconomical hardwoods. Farmers spread it on fence lines.

Of Cherokee County's 117,000 hectares (290,000 acres), more than 39,000 hectares (97,000 acres) belong to the U.S. Forest Service and Bowater Southern Paper Co. Both dump thousands of tons of Tordon on this land each year.

Tordon was first introduced in 1965, and is right on schedule as a killer, its opponents allege, since the latency period for cancer to develop from a carcinogenic agent is generally viewed as 10 to 20 years. The scientific community has so far remained divided on the question of picloram's alleged carcinogenicity.

Meanwhile, Cherokee's cancer siege is terrifying people in this isolated stretch of Appalachia. "You know this used to be a paradise," said Helen Dockery, 49, who lost both her breasts to cancer a year ago. "But no more. Everybody's sick. Every other house has cancer nearly. I don't know what's happening here."

In a 200-family stretch of the county's Hanging Dog community, where Dockery lives, 18 people were struck by cancer between January 1980 and January 1982. Six people died from it, including a 25-year-old man.

Same story

Throughout Cherokee, the story's the same. In the southwestern corner of the county, 17 people from 130 families have been stricken with cancer since January 1980. Five people died. In the local school, two teachers have skin cancer; a child in the first grade has lung cancer.

In many other places where picloram has been used, residents are charging it with causing cancer sicknesses and death. Lawsuits are pending in Oregon, Massachussetts, Alabama, Georgia, North Carolina, Tennessee, West Virginia and elsewhere.

Hardest hit are the southern states, where Tordon use is the heaviest. The Tennessee Valley Authority (TVA), the federal government's monstrous power company which operates in seven southern states, annually sprays 19,500 kilograms (43,000 pounds) of picloram from the air to clear 160 miles of transmission lines and thousands of acres of woodlands. Each year the U.S. Forest Service uses almost 19,500 kilograms (49,000 pounds) of Tordon on 31,000 hectares (77,000 acres) of national forest.

International Paper Co. uses 72,500 kilograms (160,000 pounds) of Tordon on 3,240 hectares (8,000 acres) of timberlands in seven southern states each year. Union Camp Corp. annually spreads 1,080 kilograms (2,400 pounds) of Tordon across 1,214 hectares (3,000 acres) in five southern states. Westvaco Corp., Bowater North America Corp., Champion International and Georgia Pacific — huge paper companies with extensive land holdings throughout the South — apply thousands of kilograms of Tordon to vast tracts of timberlands in every southern state.

The Environmental Protection Agency (EPA), which registers over 2,000 pesticides, classifies Tordon as one of 37 "restricted-use" pesticides but does not consider it a carcinogen. Tordon may be applied only by trained applicators who hold a special use permit. Four ounces will kill a centuries-old oak in less than a month.

Challenged studies

The controversy over picloram has spread to the National Cancer Institute (NCI), where one of the nation's top pathologists, Dr. Melvin Reuber, challenged studies commissioned by EPA and NCI which gave the chemical a clean bill of health. Reuber, who had successfully identified several questionable chemicals as carcinogens in his 10 years at NCI, was subsequently forced to resign when he spoke out publicly against the use of Malathion in California to kill Mediterranean fruit flies.

In 1979, Reuber wrote a paper called Carcinogenicity of Picloram, published in the Journal of Toxicology and Environmental Health, after he had reviewed hundreds of tissue slides prepared by researchers hired by the federal government.

Where they found no malignancies, Reuber saw one after another, cancers that spread through the bodies of rats fed doses of picloram. Said Reuber, "It doesn't surprise me that high rates of cancer are being found in Cherokee County. If the rat studies are any indication, picloram is terribly dangerous. It's highly likely Tordon is a cause for what's happening."

Dow spokesman Robert Charlton defended the continued use of Tordan. "We feel it's safe," he said, adding that his company had "severe problems" with allegations against the chemical.

The questions recently raised, however, have triggered a full EPA reanalysis of existing picloram data. The study should be be finished by September.

In the meantime, the TVA, the U.S. Forest Service, electrical power companies and paper companies continue to apply Tordon to millions of acres of rainy territory throughout the southern United States. Instructions on Tordon labels warn against using the chemical where ground water flows less than 10 feet below the surface or within half a mile of a stream used for any domestic purpose: "Do not allow Tordon to contaminate water used for drinking, irrigation, or other domestic purpose."

Dr. Ruth Shearer, a molecular biologist and former program director for cancer research at the Issaquah (Washington) Health Research Centre, has been studying the toxic effects of picloram for the past two years as a private consultant and has since been brought by the defendants into several of the legal suits involving picloram.

In Tellico Plains, Tenn., just 60 miles west of Cherokee County, Shearer interviewed members of the Ernest West family. The Wests have sued Dow Chemical and the U.S. Forest Service for $14 million, charging that a Forest Service timber crew used Tordon-101 during the summer of 1978 on an area above their home that is part of the Cherokee National Forest. Ernest West said Tordon, carried off the mountain slopes by heavy rains, has poisoned the family spring. West's attorney, Ward Welchel of Knoxville, said that West and his family have suffered from an assortment of disabling health problems, which include possible brain damage to an 8-year-old granddaughter.

Deny responsibility

Dow and the Forest Service vigorously deny responsibility for the family's ailments.

"Picloram is completely safe for humans," said Wendell Mullison, a retired Dow researcher retained by Dow as a consultant. "You know table salt is three times more toxic."

Shearer doesn't believe them. "What I'm seeing with picloram poisonings are patterns of chronic symptoms — headaches, problems with vision, weakness and fa... skin ailments, enlarged livers, ... ratory difficulties, extensive k... damage. I know Dow says picloram is three times less toxic than salt. But salt doesn't cause damage like this, and it doesn't cause cancer.

"The EPA says it's safe, b... their assumption on a group o... sense reports. They ignore ... cases around the country.

The EPA bases its opinion of Tordon's safety on three cancer research studies now being ser... questioned by environment... The first two studies were per... ed by industrial Bioset Labora... in Illinois. Last summer, Dr. Joseph Calandra, the lab's former president, and three of Calandra's assistants were indicted by the federal government for falsifying data, fabri... test results and substituting ... test animals when the origina... mals died. The Bioset studi... picloram were among a group of 160 pesticide/herbicide analyses that were found to be so deficient as to be rendered invalid. Industrial B... was subsequently shut down.

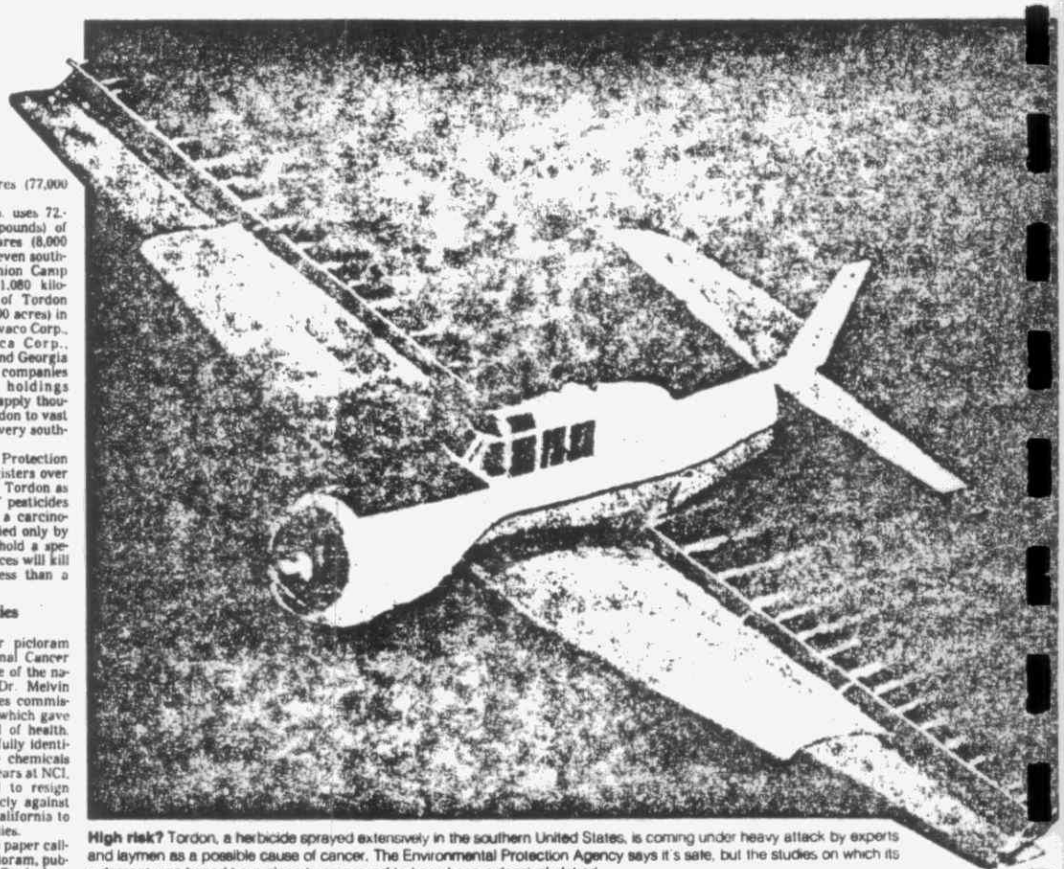
Being repeated

William Burnam, deputy chief of EPA's toxicology branch, said the picloram studies are being repeated. Asked which laboratory was ... the work, Burnam said, "D... doing the research."

The other picloram research ... conducted by Gulf South Research Institute in New Iberia, La., under contract to the National Cancer Institute. In 1977, the same year Gulf South completed its cancer res... on picloram, the EPA audite... lab. The investigators found "s... deficiencies" in Gulf South's p... dures.

These very studies, however, constitute the majority of evidence on picloram's behalf when residents of Cherokee County challenged the use of Tordon.

NEXT: ...



High risk? Tordon, a herbicide sprayed extensively in the southern United States, is coming under heavy attack by experts and laymen as a possible cause of cancer. The Environmental Protection Agency says it's safe, but the studies on which its judgment was based have since been proved to have been extensively faked.

Ontario agencies heavy users

By Rick Hallechuk Toronto Star

Ontario Government agencies are heavy users of a herbicide which studies in the United States suggest may cause cancer.

The Ministry of Transportation and Communications (MTC) and Ontario Hydro are the two big users of the chemical picloram, which is sold under the trade name Tordon. They use it to control weeds and brush along highways and hydro tower rights-of-way.

The Ministry of the Environment restricts the application of the herbicide to licensed people only, and then, only with a special ministry permit.

27 permits issued

Last year, the ministry issued 27 permits for the use of about 190,000 litres (41,800 gallons) of Tordon-101, a liquid, and 7,500 kilograms (16,500 pounds) of Tordon 10K pellets.

The amounts were broken down as follows:

- Hydro: 15 permits for 120,378 litres (26,582 gallons) for use on 6,986 hectares (17,262 acres).
- MTC: Three permits for 12,846 litres (2,825 gallons) for weed spraying on 2,257 hectares (5,576 acres), mostly in Southern Ontario, and 56,002 litres (12,318 gallons) for brush spraying on 2,467 hectares (6,095 acres), mainly in Northern Ontario.
- The Ministry of Natural Resources: Six permits for 754 litres (165 gallons).
- Great Lakes Paper Co., one permit for 168 litres (36 gallons).
- Sturgeon Falls Brush Spraying and Cutting Ltd.: One permit for 1,000 litres (219 gallons).
- CP Rail: One permit for 7,500 kilograms (16,534 pounds).

Only the MTC figures are for amounts actually used in 1981; the others are maximum figures allowed under permits.

Lorna Poff, of the Ministry of the Environment's pesticides control section, says she hasn't seen any studies conclusively linking picloram with cancer.

"I'm going to look into it, of course," Poff told The Star. "I'll call people in the (U.S.) Environmental Protection Agency and the National Cancer Institute."

But Poff pointed out that research done in the United States by pathologist Melvin Reuber is merely a re-examination of research done by others.

EPA studies said the chemical was safe, Poff noted.

Two years ago this month the ministry banned the use of the herbicide 2,4,5T following similar action in the United States, based on a study linking its use to abnormally high rate of miscarriages in Oregon.

But picloram isn't as dangerous as 2,4,5T, says Alex Chisholm, executive secretary of the environment ministry's Pesticides Advisory Committee.

"I don't think any pesticide is safe — it has to be handled properly — but I'm not aware of any hazard to humans" from picloram, Chisholm said in an interview.

Use increased

Poff said she couldn't be sure but suspects that the use of picloram increased after 2,4,5T was banned.

Environment Minister Keith Norton was unaware of the alleged problems with picloram in the United States but promised to look into them.

Norton also made the point that picloram is registered for use by the federal government, which requires studies into long-term effects of chemicals.

"As in the case of many of these chemicals, there are hazards associated with careless or improper use — hence, the careful control," he said.

Poff says the picloram in Ontario is not sprayed from the air, as in many cases in the United States, but applied on the ground.

DR. MEL REUBER, PATHOLOGIST, GETS SHARP CENSURE, WARNING FROM HIS SUPERVISOR

Dr. Melvin D. Reuber, a pathologist repeatedly involved with pesticide carcinogenicity studies and interpretation of study results and slides, has been censured by his supervisor for general unprofessional conduct and charged with specific "obstreperous actions (which) have had a multi-million dollar implication, giving the impression that the NCI (National Cancer Institute) may be administering programs of questionable competency."

"These actions are unfortunate; your carelessness and lack of professional expertise in dealing with these issues have seriously prevented any real technological issues from being addressed in a sound scientific manner," the "admonishment" to Dr. Reuber from Dr. M. G. Hanna, Jr., Director of the Frederick Cancer Research Center (FCRC), charged. FCRC is operated for NCI by Litton Bionetics, Inc. Dr. Reuber is Head, Experimental Pathology/Histotechnology Laboratory, FCRC (See Jan. 10, 1979, Page 7).

"Obstreperous actions" and specific charges levied against Dr. Reuber by Dr. Hanna included: Mishandling and unrestrained interpretations of scientific data which in part created "public distrust and lack of confidence in the National Cancer Institute (NCI) authorities who administer the carcinogenesis testing program;" operating under the "guise of the endorsement" of NCI and FCRA; and disputing the competency of tests and the pathologists associated with them. Dr. Hanna's letter to Dr. Reuber stated:

"The allegations which have been brought against you (which I have investigated and have found to be true) are that you have reinterpreted slides that were part of several bioassay carcinogenicity tests including those tests associated with malathion, malaoxon, and picloram. With regard to malathion and malaoxon, your statement in a letter to Mr. Rominger, the Director of the Department of Food and Agriculture in Sacramento, California, was that your reinterpretation was based on "examination of every histological slide," (up to 24,000 slides) of the three studies. Based on this statement, and assuming that a competent pathologist would spend a minimum of five minutes per slide in order to adequately reinterpret a previous diagnosis, you spent a total of 333 days in the repositary reading these slides. I have checked the repository records and you have not spent that amount of time in the repository. Therefore, I can only assume that your statement regarding your thorough evaluation of these slides was incorrect and misleading. On the other hand, you may have spent considerably less time per slide, thus raising a question of whether your interpretation is scientifically valid."

Dr. Hanna said he was giving Dr. Reuber a "very firm warning" rather than terminating him even though grounds to do so were apparent. A particular ground was that Dr. Reuber's scientific communications and publications were not reviewed through the NCI system, since in your own words, Dr. Hanna noted, the papers would 'not have gotten through the system.' I can only assume this statement to mean that you knew your comments would not have passed critical scientific review and evaluation. You nevertheless used these materials to create a political and economic controversy to the discredit of the NCI Carcinogenesis Testing Program, and misrepresented the publications as having the endorsement of both the NCI and the contractor of FCRC, Litton Bionetics, Inc." The letter to Dr. Reuber continued:

"I find this to be the most flagrant professional absue that I have ever experienced in my scientific and administrative career. You have violated a signed employment agreement that you had with the FCRC when you joined the staff, acknowledging that you would adhere to the publication policies as well as all other policies. Your blatant disregard for these agreements is grounds for immediate termination. I will not use this administrative prerogative, however, because due to the sensitivity of the issues, your termination could be easily misinterpreted: the public confidence in scientists and scientific procedures for communications of results is a valuable and cherished trust. When scientists abuse and misrepresent this trust for whatever reasons, sincere or insincere, I feel it must be dealt with internally rather than simply excised, possibly to return at a later time."

The FCRC Director specifically warned Dr. Reuber that "as of now you are not to use compensatory time away from the laboratory for any purpose unless it is cleared by me." The letter to Dr. Reuber continued:

"Furthermore, all publications that you are associated with are to adhere to the rigid policy of internal scientific review and clearance through my office and through the National Cancer Institute administrative offices. Any divergence from either of these policies or any other policies associated with the FCRC, and any reduction in your present work effort will be grounds for immediate termination from the Frederick Cancer Research Center. This regrettable situation has been created by your arrogant lack of concern for scientific and administrative policies at the Center and at the National Cancer Institute. You exploited the privilege of scientific communication in an unrestrained manner. You have pontificated and criticized other scientists in a manner that excited the public in areas of immediate national concern. Rather than using the forum accepted by scientists, you have used an unreviewed forum to gain easy and immediate voice to the media where public health issues are most easily sensationalized. You may be correct in your interpretations, but the rest of the scientific community, and the public, has not had the advantage or privilege of learning and evaluating your view since you declined to pass it through the standard review procedure established for this purpose. Therefore, neither the scientific community nor the public has adequately benefited from your important information and viewpoint. This is counterproductive at all levels.

"You are a good pathologist and have a lot to offer the carcinogenesis testing program. My goal is to harness your efforts in a meaningful manner and direct them such that the taxpayer benefits from your expertise, rather than becoming excited or biased by your misuse of your position and your credentials ... I am not interested in thwarting your efforts on behalf of public concern for environmentally mediated health problems, but rather, espouse to channel these efforts in a legitimate manner that will gain the respect and support of all parties concerned."

According to the letter, Dr. Reuber's stand on malathion and malaoxon challenged and question the competency of pathologists at the Gulf South Research Institute, New Iberia, La., who were under contract to NCI.